Michael Hale et al.

Application No.:

10/688,613

## **AMENDMENTS TO THE CLAIMS**

Please replace all prior versions and listings of claims with the amended claims as follows:

1. (Currently amended) A compound of formula I:

I

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:  $R^1$  is selected from R, halogen,  $N(R^8)_2$ , OR, NRCOR,

NRCON(R<sup>8</sup>)<sub>2</sub>, CON(R<sup>8</sup>)<sub>2</sub>, SO<sub>2</sub>R, NRSO<sub>2</sub>R, or SO<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>;

T is selected from a valence bond or a linker group selected from -O-, -S-, -NH<sub>2</sub>-, or an optionally substituted C<sub>1-6</sub> alkylidene chain, wherein up to two saturated carbons of the chain are optionally replaced by -C(=O)-, -CONH-, CONHNH-, -CO<sub>2</sub>-, -NHCO<sub>2</sub>-, -O-, -NHCONH-, -OC(=O)-, -OC(=O)NH-, -NHCO-, -O-, -S-, -SO-, -SO<sub>2</sub>-, -NH-, -SO<sub>2</sub>NH-, or NHSO<sub>2</sub>-;

each R is independently selected from hydrogen or an optionally substituted aliphatic group having one to six carbons;

R<sup>2</sup> is selected from hydrogen, CN, halogen, aryl, aralkyl, heteroaryl, heterocyclyl, an optionally substituted acyclic aliphatic chain group having one to six carbons, or an optionally substituted cyclic aliphatic group having four to ten carbons;

R<sup>3</sup> is selected from R, OH, OR, N(R<sup>8</sup>)<sub>2</sub>, halogen, or CN;

Q is a valence bond, J, or an optionally substituted  $C_{1-6}$  alkylidene chain wherein up to two nonadjacent carbons of the alkylidene chain are each optionally and independently replaced by J;

Michael Hale et al.

Application No.:

10/688,613

J is selected from -C(=O)-, -CO<sub>2</sub>-, -C(O)C(O)-, -NRCONR<sup>8</sup>-, -N(R)N(R<sup>8</sup>)-,
-C(=O)NR<sup>8</sup>-, -NRC(=O)-, -O-, -S-,-SO-, -SO<sub>2</sub>-, -N(R)O-, -ON(R<sup>8</sup>)-,
-OC(=O)N(R<sup>8</sup>)-, -N(R)COO-, -SO<sub>2</sub>N(R<sup>8</sup>)-, -N(R)SO<sub>2</sub>-, or -N(R<sup>8</sup>)-;
R<sup>4</sup> is selected from -R<sup>8</sup>, -R<sup>5</sup>, -NH<sub>2</sub>, -NHR<sup>5</sup>, -N(R<sup>5</sup>)<sub>2</sub>, or -NR<sup>5</sup>(CH<sub>2</sub>)<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>;

R' is selected from  $-R^5$ ,  $-R^7$ ,  $-NH_2$ ,  $-NHR^3$ ,  $-N(R^3)_2$ , or  $-NR^3(CH_2)_yN(R^3)_2$ ; each  $R^5$  is independently selected from  $R^6$ ,  $R^7$ ,  $-(CH_2)_yCH(R^6)(R^7)$ ,  $-(CH_2)_yR^6$ ,

 $-(CH_2)_yCH(R^6)_2$ ,  $-(CH_2)_yCH(R^7)_2$ , or  $-(CH_2)_yR^7$ ;

y is 0-6;

each R<sup>6</sup> is an optionally substituted group independently selected from an aliphatic, aryl, aralkyl, aralkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, heterocyclylalkoxy, group;

each R<sup>7</sup> is independently selected from an optionally substituted aliphatic, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, or alkoxycarbonyl;

- each R<sup>8</sup> is independently selected from R, or two R<sup>8</sup> on the same nitrogen taken together with the nitrogen optionally form a four to eight membered, saturated or unsaturated heterocyclic ring having one to three heteroatoms;
- and each substitutable ring nitrogen is optionally substituted by R, NR<sub>2</sub>, COR, CO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> optionally substituted alkyl), CONR<sub>2</sub>, and SO<sub>2</sub>NR<sub>2</sub>; provided that QR<sup>4</sup> is other than CON(CH<sub>3</sub>)<sub>2</sub> when R<sup>1</sup> and R<sup>3</sup> are each hydrogen and when TR<sup>2</sup> is an unsubstituted phenyl ring attached at the 4-position of the pyrazole ring.
  - 2. (Original) The compound according to claim 1 having the formula

П

or a pharmaceutically acceptable derivative or prodrug thereof.

Michael Hale et al.

Application No.:

10/688,613

3. (Original) The compound according to claim 2 having one or more of the following features: (a) Q is -CO<sub>2</sub>-, or

-CONH-; (b) T is a valence bond; (c)  $R^1$  is hydrogen or NHR; (d)  $R^2$  is an optionally substituted aryl ring; (e)  $R^3$  is hydrogen; (f)  $R^4$  is selected from  $R^5$ , -NHR<sup>5</sup>, -N( $R^5$ )<sub>2</sub>, -NR<sup>5</sup>R<sup>6</sup>, -NHCHR<sup>5</sup>R<sup>6</sup>, or -NHCH<sub>2</sub>R<sup>5</sup>; or (g)  $R^5$  is an optionally substituted group selected from aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl group, (CH<sub>2</sub>)<sub>y</sub>R<sup>6</sup>, (CH<sub>2</sub>)<sub>y</sub>R<sup>7</sup>, or (CH<sub>2</sub>)<sub>y</sub>CH(R<sup>6</sup>)(R<sup>7</sup>).

4. (Original) The compound according to claim 3 having the formula

II-A

or a pharmaceutically acceptable derivative or prodrug thereof.

- 5. (Original) The compound according to claim 4 having the following features: (a) T is a valence bond; (b)  $R^2$  is an optionally substituted aryl ring; (c)  $R^4$  is selected from  $R^5$ , -NHR<sup>5</sup>, -N( $R^5$ )<sub>2</sub>, -NR<sup>5</sup>R<sup>6</sup>, -NHCHR<sup>5</sup>R<sup>6</sup>, or -NHCH<sub>2</sub>R<sup>5</sup>; and (d)  $R^5$  is an optionally substituted group selected from aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl group,  $(CH_2)_yR^6$ ,  $(CH_2)_yR^7$ , or  $(CH_2)_yCH(R^6)(R^7)$ .
- 6. (Currently amended) The compound according to claim I wherein said compound is selected from those listed in Table 1: , said compound being other than compound number 1.

Michael Hale et al.

Application No.:

10/688,613

11

No.	T-R <sup>2</sup>	0.74
		Q-R <sup>4</sup>
II-2	phenyl	CO₂Et
II-3	3-NO <sub>2</sub> -phenyi	CONHNH₂
П-6	3-NO <sub>2</sub> -phenyl	CO₂Et
II-7	4-Cl-phenyl	CO₂Et
¥1-8	4-OMe-phenyl	CO₂Et
11-9	3-NH <sub>2</sub> -phenyl	CO2Et
II-10	3-OMc-phenyl	CO₂Et
П-11	4-F-phenyl	CO₂Et
П-12	4-NO <sub>2</sub> -phenyl	CO <sub>2</sub> Et
П-13	3-Cl-phenyl	CO <sub>2</sub> Et
11-14	3-F-phenyl	CO₂Et
П-15	phenyl	CO <sub>2</sub> H
П-16	4-NH <sub>2</sub> -phenyl	CO <sub>2</sub> Et
II-17	phenyl	CONHCH2CH2N(Me)2
II-20	phenyl	CONH(isopropyl)
II-23	3-OMe-phenyl	CONMe <sub>2</sub>
II-25	3-OMc-phenyl	CONHCH2CH2N(Me)2
II-31	4-NH <sub>2</sub> -phenyl	CO <sub>2</sub> Et
II-32	Н	CONMe <sub>2</sub>
П-34	3-(AcNH)-phenyl	CO₂Et
II-35	4-(AcNH)-phenyl	CO <sub>2</sub> Et
II-36	3-(AcNH)-phenyl	CO <sub>2</sub> Et
II-37	4-(AcNH)-phenyl	CO <sub>2</sub> Et
<b>II-4</b> 5	5-Br-phenyl	CONH(2-OH-1-Ph-ethyl)
11-66	3,5-Cl <sub>2</sub> -phenyl	CON(Me)(Et)

Michael Hale et al.

Application No.:

No.	T-R <sup>2</sup>	Q-R⁴
<b>II</b> -71	4-F-5-Cl-phenyl	CON(Me)(Et)
11-81	5-Cl-6-F-phenyl	CON(Me)(Et)
II-83	5-Br-phenyl	ئاب^ن
II-93	5-Cl-phenyl	CON(Me)(Et)
II-108	4-F-5-Cl-phenyl	CON(Me)(Et)
II-130	5-Br-phenyl	CONHCH2CH2OH
<b>II-</b> 137	5-NO <sub>2</sub> -phenyl	CONH <sub>2</sub> NH <sub>2</sub>
II-139	5-Br-phenyl	y l NOH
II-143	phenyl	CON(Me) <sub>2</sub>
II-148	5-NO <sub>2</sub> -phenyl	COOEt
II-151	5-Cl-phenyl	COOEt
П-152	5-Br-phenyl	CONHMe
II-154	5-OMe-phenyl	CON(Me) <sub>2</sub>
П-156	5-Br-phenyl	3- NOH
<b>II-</b> 157	5-Br-phenyl	COOEt
II-158	phenyl	CONH(iPt)
II-159	5-OMe-phenyl	CONH(iPr)
II-160	5-COOH-phenyl	CONH(iPr)
II-161	5-Br-phenyl	CONHO(iPr)
II-162	5-F-phenyl	COOEt
11-164	4-NH <sub>2</sub> -phenyl	COOEt
II-165	4-NO <sub>2</sub> -phenyl	COOEt
II-167	4-Cl-phenyl	COOEt
II-168	4-OMe-phenyl	COOEt
11-169	phenyl	COOEt

Michael Hale et al.

Applicants:
Application No.:

No.	T-R <sup>2</sup>	Q-R <sup>4</sup>
II-170	5-OMe-phenyl	COOEt
11-171	4-F-phenyl	COOEt
11-172	5-NH <sub>2</sub> -phenyl	COOEt
II-173	5-Cl-phenyl	СООН
II-237	5,6-F <sub>2</sub> -phenyl	CON(Me)(Et)
II-258	4,5-(OMe) <sub>2</sub> -phenyl	CON(Me)(Et)
II-262	4-benzo[1,3]dioxo-5-yl	CON(Me)(Et)
II-280	5-Br-phenyl	CONH(CH <sub>2</sub> ) <sub>2</sub> COOH
П-282	5-Br-phenyl	CONHCH2(4-COOH-phenyl)
п-288	5-Br-phenyl	2 NOH
II-290	5-Br-phenyl	yin C
II-291	5-F-phenyl	CON(Me)(Et)
II-292	5-MeO-phenyl	CON(Me)(Et)
П-295	5-Br-phenyl	SHOH OH OH OH
II-296	5-Br-phenyl	OMe OMe OH H
II-297	phenyl	CONH(CH <sub>2</sub> ) <sub>2</sub> NMe <sub>2</sub>
П-298	5-MeO-phenyl	CONH(CH <sub>2</sub> ) <sub>2</sub> NMe <sub>2</sub>
II-323	CH₂Ph	CON(Me) <sub>2</sub>
II-325	isopropyl	CN

Michael Hale et al.

Application No.:

10/688,613

No.	T-R <sup>2</sup>	Q-R <sup>4</sup>
II-326	3-Cl-phenyl	NHCOCH <sub>2</sub> Ph
II-328	3-Cl-phenyl	NHCONHCH₂Ph
П-329	3-Cl-phenyl	NHCO <sub>2</sub> -tetrahydrofuran-2-yl
II-333	Н	CON(Me) <sub>2</sub>

7. (Original) The compound according to claim 1 having the formula:

II-B

or a pharmaceutically acceptable derivative or prodrug thereof.

- 8. (Original) The compound according to claim 7 wherein said compound has one or more of the following features: (a) T is a valence bond; (b)  $R^2$  is an optionally substituted aryl ring; (c)  $R^4$  is selected from  $R^5$ , -NHR<sup>5</sup>, -N( $R^5$ )<sub>2</sub>, -NR<sup>5</sup>R<sup>6</sup>, -NHCHR<sup>5</sup>R<sup>6</sup>, or -NHCH<sub>2</sub>R<sup>5</sup>; or (d)  $R^5$  is an optionally substituted group selected from aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl group, (CH<sub>2</sub>)<sub>y</sub>R<sup>6</sup>, (CH<sub>2</sub>)<sub>y</sub>R<sup>7</sup>, or (CH<sub>2</sub>)<sub>y</sub>CH(R<sup>6</sup>)(R<sup>7</sup>).
- 9. (Currently amended) The compound according to claim 1 wherein said compound is selected from those listed in Table 2: [[.]]

Michael Hale et al.

Application No.:

No.	R	T-R <sup>2</sup>	Q-R⁴
II-B-1	Н	phenyl	CON(Me) <sub>2</sub>
11-B-2	H	- phenyl	CO <sub>7</sub> Et
П-В-3	Н	3-NO <sub>2</sub> -phenyl	CONHNH <sub>2</sub>
II-B-6	Н	3-NO <sub>2</sub> -phenyl	CO <sub>2</sub> Et
II-B-7	H	4-Cl-phenyl	CO <sub>2</sub> Et
II-B-8	Me	4-OMe-phenyl	CO₂Et
II-B-9	H	3-NH <sub>2</sub> -phenyl	CO <sub>2</sub> Et
II-B-10	H	3-OMe-phenyl	CO <sub>2</sub> Et
I-B-11	H	4-F-phenyl	CO <sub>2</sub> Et
I-B-12	н	4-NO <sub>2</sub> -phenyl	CO <sub>2</sub> Et
I-B-13	_ Et	3-Cl-phenyl	CO <sub>2</sub> Et
П-В-14	н	3-F-phenyl	CO <sub>2</sub> Et
I-B-15	H	phenyl	CO <sub>2</sub> H
II-B-27	H	Н	CON(Me) <sub>2</sub>

- 10. (Original) A composition comprising a compound according to any one of claims 1 to 9 in an amount sufficient to detectably inhibit protein kinase activity, said protein kinase selected from one or more of ERK, JAK, JNK, Aurora, GSK, KDR, AKT, or a protein kinase related thereto; and a pharmaceutically acceptable carrier.
- 11. (Original) The composition according to claim 10 wherein said compound is formulated in a pharmaceutically acceptable manner for administration to a patient.
- 12. (Original) A composition according to either of claims 10 or 11 further comprising a therapeutic agent, either as part of a multiple dosage form together with said compound or as a separate dosage form.
- 13. (Original) A method of inhibiting protein kinase activity in a biological sample, wherein said protein kinase is selected from ERK, JAK, JNK, Aurora, GSK, KDR, AKT, or a protein kinase related thereto, comprising the step of contacting said sample with a compound according to any one of claims 1 to 9.

Michael Hale et al.

Application No.:

- 14. (Original) A method for treating a protein kinase-mediated disease state in a patient, wherein said protein kinase is selected from one or more of ERK, JAK, JNK, Aurora, KDR, AKT, or a protein kinase related thereto, comprising the step of administering to said patient a composition according to claim 11.
- 15. (Original) The method according to claim 14, comprising the additional step of administering to said patient a therapeutic agent either as part of a multiple dosage form together with said compound or as a separate dosage form.
- 16. (Original) A method of treating a disease state in a patient, wherein said disease state is selected from cancer, stroke, diabetes, hepatomegaly, cardiovascular disease, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders, inflammation, neurological disorders, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukemia (CML), liver disease, pathologic immune conditions involving T cell activation, or CNS disorders, comprising the step of administering to said patient a composition according to claim 10.
- 17. (Original) The method according to claim 16 wherein the disease state is cancer.
- 18. (Original) The method according to claim 17 wherein the disease state is a cancer selected from breast; ovary; cervix; prostate; testis, genitourinary tract; esophagus; larynx, glioblastoma; neuroblastoma; stomach; skin, keratoacanthoma; lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma; bone; colon, adenoma; pancreas, adenocarcinoma; thyroid, follicular

Michael Hale et al.

Application No.:

10/688,613

carcinoma, undifferentiated carcinoma, papillary carcinoma; seminoma; melanoma; sarcoma; bladder carcinoma; liver carcinoma and biliary passages; kidney carcinoma; myeloid disorders; lymphoid disorders, Hodgkin's, hairy cells; buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx; small intestine; colon-rectum, large intestine, rectum; brain and central nervous system; or leukemia.

- 19. (Original) The method according to either of claims 17 or 18 comprising the additional step of administering to said patient a chemotherapeutic agent either as part of a multiple dosage form together with said compound or as a separate dosage form.
- 20. (Original) The method according to claim 16 wherein the disease state is cardiovascular disease.
- 21. (Original) The method according to claim 20 wherein the disease state is a cardiovascular disease selected from restenosis, cardiomegaly, artherosclerosis, myocardial infarction, or congestive heart failure.
- 22. (Original) The method according to either of claims 20 or 21 comprising the additional step of administering to said patient a therapeutic agent for treating cardiovascular disease either as part of a multiple dosage form together with said compound or as a separate dosage form.
- 23. (Original) A composition for coating an implantable device comprising a compound according to claim 1 and a carrier suitable for coating said implantable device.
- 24. (Original) An implantable device coated with a composition according to claim 23.